AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,085	07/11/2002	David W. Sammons	6033-001	6300

7590 10/14/2005

David G Rosenbaum
Rosenbaum & Associates
Suite 3600
875 North Michigan Avenue
Chicago, IL 60611

EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,085	SAMMONS ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 December 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims Under Prosecution

1. Claims 1-10 are pending. All claims 1-10 are under examination.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The prior-filed application is US Provisional Patent Application Serial No. 60/137,692, which was filed on June 4, 1999 upon which the instant application is a continuation-in-part of.

It is noted that the subject matters of 1) enriching nucleated fetal erythrocytes by charge flow separation to remove a major fraction of platelets and mature erythrocytes without substantial loss of nucleated erythrocytes (recited in claims 2, 3, and 4); and 2) storing digitized images and plurality of coordinates onto a web-based internet server for remote access and manipulation of the stored digitized images (recited in claim 1) are not disclosed and described in ASN 60/137,692 from which the benefit of priority is claimed. As these subject matters are only disclosed in the instant National Stage application, for purposes of priority, claims 1-4 have been granted a priority date of July 11, 2002, which is the "filing fate" at which the last of the 35 USC 371 requirements of this National Application is met by Applicant and received by the Office. As subject matters encompassing histochemical staining, phenotype labeling, karyotype labeling, detection, and imaging are disclosed and described in the provisional application and

recited in claims 5-10 in this National Stage application, claims 5-10 will have the benefit of priority of the provisional application SN 60/137,692 having a filing date of June 4, 1999.

Drawings

3. The drawings are objected to because the legend defining Figure 14 is misspelled, i.e. "Cell Imag". It should be changed to "Cell Image". Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is unclear as to whether the step of, "obtaining a maternal whole blood sample ..." is intended to be part of the claimed method. As written, it does not appear to have been incorporated as part of the preamble; however, no identifying designation, i.e. step a) or step b), has been assigned thereto. Alternatively, it appears that it should be part of the claimed method as the recitation provides an actual active method step of a procedure.

Claim 1, step c) has improper antecedent basis problem in reciting, "with detectable label". Change to "with the detectable label" for proper antecedent basis.

Claim 1, step d) has improper antecedent basis problem in reciting, "labeled nucleated fetal erythrocytes". Change to "the labeled nucleated fetal erythrocytes" for proper antecedent basis.

Claim 1 is vague and indefinite in reciting, "A prenatal diagnostic method" in the preamble, because it is unclear how the claimed method, as recited, is a "diagnostic" method. At best, the method steps appear to only provide identification of enriched fetal nucleated cells from a maternal whole blood sample; which if isolated, identified, and

imaged, can be used to provide genotypic and phenotypic characterization of the fetal nucleated erythrocytes to hence, provide a diagnostic capability. Please clarify.

Claim 2 is vague in reciting, "wherein the step of enriching *further comprises* the step of centrifugation" because it is unclear as to whether the step of centrifugation is a separate step that *further comprises* the enriching step, or does the centrifugation step intend to encompass the enriching step. If the former statement is true, then it is unclear what the "enriching step" is intended to encompass. If the latter statement is true, then claim 2 should recite, "wherein the step of enriching *comprises* the step of centrifugation".

Claim 4 is vague in reciting, "wherein the step of charge flow separation *further comprises* the step of imparting a buffer flow through a charge flow separator" because it is unclear as to whether the step of imparting a buffer flow through a charge flow separator is a separate step that *further comprises* the step of charge flow separation, or does the step of imparting a buffer flow through a charge flow separator intend to encompass the step of charge flow separation. If the former statement is true, then it is unclear what the "step of charge flow separation" is intended to encompass. If the latter statement is true, then claim 4 should recite, "wherein the step of charge flow separation *comprises* the step of imparting a buffer flow through a charge flow separator".

Claim 4 is objected to for the recitation of "an flow orientation vector". Claim 4 should properly recite, "a flow orientation vector".

Claim 5 is confusing in reciting "wherein the labeling step *further comprises* the step of binding a fetal cell-specific antibody" because it is unclear what structural and

functional cooperative relationship exists between the "fetal cell-specific antibody" in the instant claim and the "detectable label" recited in claim 1. It is also specifically unclear what is encompassed by "the detectable label" in claim 1 and how it relates to the "binding of fetal [labeled] cell-specific antibody" which is supposed to differentially encompass a separate label from that recited in claim 1; or does Applicant intend for the "detectable label" and "[labeled] fetal specific antibody" to be the same label. If Applicant intends the labeling step of claim 1, step b) to encompass a different detectable label, i.e. histochemical stain, from the "label" recited in the instant claim, i.e. monoclonal antibody label, then such should be clearly, distinctly, and differentially defined in the claimed invention.

Claim 5 is vague and indefinite in reciting, "fetal cell-specific antibody" because it is unclear as to whether the antibody is intended to be specific for any "fetal cell", including fetal mature (non-nucleate) erythrocytes. If so, it is unclear how the antibody should only bind fetal nucleated erythrocytes. It appears that claim 5 should properly recite, "fetal nucleated erythrocyte-specific antibody."

Claim 6 is vague and indefinite in reciting, "fetal cell-specific antibody" because it is unclear as to whether the antibody is intended to be specific for any "fetal cell", including fetal mature (non-nucleate) erythrocytes. If so, it is unclear how the antibody should only bind fetal nucleated erythrocytes. It appears that claim 6 should properly recite, "fetal nucleated erythrocyte-specific antibody."

Claim 6 is confusing in relation to claim 5 from which it depends because it is unclear how "a magnetic bead" for conjugation with the "fetal cell-specific antibody" is part of the labeling step. Please clarify.

Claim 7 is confusing in relation to claim 5 from which it depends in reciting, "where the binding step is followed by binding a fluorescent label" because it is unclear how "binding a fluorescent label" is effected within the labeling step. Does Applicant perhaps intend that the "fetal cell-specific antibody" is conjugated with a fluorescent label. It is specifically unclear what structural and functional cooperative relationship exists between this instant "fluorescent label", the "fetal cell-specific antibody" recited in claim 5, and the "detectable label" recited in claim 1, both from which the instant claim 7 depends. Does Applicant intend for all these "labels" to encompass one same label. If Applicant intends the labeling step of claim 1, step b) to encompass a different detectable label, i.e. histochemical stain, from the "label" recited in claim 5, i.e. monoclonal antibody label, and further from the "fluorescent label" in the instant claim, i.e. fluorescent FISH probe, then such should be clearly, distinctly, and differentially defined in the claimed invention. Please clarify.

In sum, if each of the "labeling elements" recited in claims 1, 5, and 7 are intended to be distinct elements, then all of claims 1, 5, and 7 should clearly, distinctly, and differentially define them as such, providing how one element directly or differentially relates from another. As an example, if Applicant intends the label in claim 1 to be a histochemical stain (DAPI for identifying DNA in nuclei), the label in claim 5 to be a fluorescent labeled monoclonal antibody (labeled fetal nucleated erythrocyte-

specific antibody for fetal nucleated red cell phenotyping), and the label in claim 7 to be a fluorescent in situ hybridization (FISH) probe (for karyotyping or genotyping X and Y chromosomes), it is suggested that each element be defined as such or equivalent language be used, to assist Applicant in obviating these indefiniteness issues. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim 9 lacks antecedent basis in reciting, "the labeled features".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Since claims 1-10 are so unclear and broad, as to the type, number, nature, and relationship of detectable labels used, the recitation of "detectable label", "[labeled] fetal cell-specific antibody", and "fluorescent label" within the context of the labeling steps in claims 1, 5, and 7, respectively, are read to encompass any one type of labeling, i.e. histochemical staining, fluorescent labeled antibody labeling, and fluorescent in situ hybridization probe labeling; alone, in combination, and in multiple versions thereof,

because unpatented claims are given the broadest interpretation consistent with the specification. Accordingly,

5. Claims 1, 2, 5, and 7-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Ravkin (US Patent 6,169,816).

Ravkin discloses optical recognition systems for identifying fetal nucleated erythrocytes or from here on, fetal nRBCs, from maternal cells. The system performs image processing of fetal nRBCs labeled with different dyes, which are caused to reside on and define different portions of the fetal nRBCs such as the fetal hemoglobin in the cytoplasm and also the nuclei (see column 1, line 65 to column 2, line 11). Ravkin discloses obtaining maternal whole blood sample containing fetal nRBCs, enriching the population of fetal nRBCs in the sample, and labeling the fetal nRBCs in the enriched sample with a detectable label (labeled anti-fetal hemoglobin nRBC antibody, VECTOR BLUE substrate, DAPI, fluorescent labeled FISH probe) for positive identification and genetic analysis of the fetal nRBCs. Ravkin uses fluorescent labeled FISH probe to bind and identify DNA in the chromosomes of the fetal nRBCs. Ravkin also discloses use of multiple FISH probes or M-FISH which are labeled with different fluorescent dyes, i.e. different detectable labels, for identifying different portions of the fetal nRBC DNA (see column 2, line 60 to column 3, line 37). The enrichment procedure comprises centrifugation of the whole blood sample to remove major fractions of platelets and mature RBCs, then nRBCs are harvested from the interface between the white blood cells (WBCs) and the RBCs. The enriched portion is also subjected to selective lysis of

maternal RBCs and three layer density gradient to separate nRBCs from WBCs (see column 2, lines 38-56). Thereafter, fetal nRBCs are labeled with anti-fetal nRBC specific antibody, i.e. anti-fetal hemoglobin nRBC antibody or anti-HbF, then with secondary antibody indirectly conjugated to alkaline phosphatase for reaction with VECTOR BLUE substrate, which gives a blue precipitate on the cytoplasm of fetal nRBCs, and a DNA intercalating agent (DAPI) that gives the nuclei a fluorescent blue stain. The presence of these contrast labels, identifies, and determines the presence of fetal nRBCs (see column 3, line 64 to column 4, line 6 and column 5, lines 42-63). The nRBCs are detected by creating digitized images or fields from enriched samples on microscope slides containing labeled nRBCs, using a CCD (charge coupled device); the digitized images are subsequently sent to a computer for processing of the digitized images. The computer includes controlling motors for positionally controlling the microscope stage and the microscope slide containing the enriched fetal nRBCs sample (see column 4, lines 52-56, column 5, lines 12-25, and column 5, line 66 to column 6, line 10). Cytological features representative of fetal nRBCs are located and determined in a plurality of fields, then a plurality of positional coordinates are assigned therefor. Images are subsequently obtained, generated, and digitized from these cytological and morphological features (see column 7, lines 10-57). Ravkin discloses storing the digitized images and coordinates onto a web-based internet server (Internet's Word Wide Web) for remote access and manipulation of the stored digitized images. The digitized images may also be stored onto machine readable medium (hard drive, floppy) (see column 6, line 59 to column 7, line 5).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ravkin (US Patent 6,169,816) in view of Sammons et al. (US Patent 5,662,813).

Ravkin has been discussed supra. Ravkin differs from the instant invention in failing to teach that the enriching step further comprises charge flow separation.

Sammons et al. disclose a method for separation and enrichment of nucleated fetal erythrocytes or from here on, fetal nRBCs from maternal blood samples using charge flow separation. Sammons et al. teach obtaining maternal whole blood sample

containing fetal nRBCs, enriching the population of nRBCs by centrifugation and Ficoll gradient layering. The nucleated cell layer obtained from the maternal blood sample, is resuspended in buffer and then subjected to charge flow separation in a charge flow separator having a flow orientation vector which is opposite to applied electrical charge vector within the charge flow separator (buffer input flow rate of 0.270 ml/min/channel with a buffer output flow rate of 0.220 ml/min/channel, and a counterflow rate of 1.8 ml/min. in applied electric field of 250 V at 68-72 mA). After enrichment by charge flow separation, fetal nRBCs are collected and identified histologically with a detectable label. See Example 1. Sammons et al. provide that enrichment method may be operated stand alone or as a pre- or post- processing step in conjunction with the charge flow separation method (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Sammons in charge flow separation (CFS) for enriching rare fetal nRBCs, into the method of enriching and detecting fetal nRBCs as taught by Ravkin having incorporated therein, automated digitized imaging, processing, and storing of the labeled and identified fetal nRBCs, because Sammons specifically suggested application of the CFS method in conjunction or combination with any other cellular separation/enrichment methods. One of ordinary skill in the art at the time of the instant invention would have been motivated to combine the teaching of Sammons which incorporate charge flow separation, with other fetal nRBC enrichment methods such as that taught by Ravkin, wherein fetal nRBCs are enriched and detected

for further automated processing of digitized images because Sammons specifically provides that the CFS method successfully recovers fetal nRBCs from the peripheral circulation of pregnant women for histological identification, and since the recovered cells are viable, the nRBCs can be subjected to further enrichment methods such as cell culture.

7. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ravkin (US Patent 6,169,816) in view of Alter (US Patent 5,580,724).

Ravkin has been discussed supra. Ravkin differs from the instant invention in failing to teach that the fetal cell-specific antibody is conjugated to a magnetic bead.

Alter discloses methods of differential expansion of fetal stem cells, including fetal nucleated erythrocytes or from here on, fetal nRBCs (erythroid progenitors), in whole blood obtained from maternal circulation for use in prenatal diagnosis purposes (see Abstract). In separation methods for separating fetal mononuclear cells, such as fetal nRBCs expressing CD71 (early erythroid cells which are nRBCs), Alter teaches incorporating magnetic beads into fetal nRBCs in order to separate and enrich the nRBCs from the maternal mononuclear cells, using magnetic activated cell sorting (MACS) (see column 8, lines 24-65). Selective enrichment is accomplished through binding or conjugation with antibodies specific for the nRBCs expressing CD71, i.e. anti-CD71 antibody conjugated to a magnetic bead (see also column 9, lines 10-34).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Alter in incorporating magnetic beads into nRBCs for enrichment processing by MACS, into the method of enriching and detecting fetal nRBCs as taught by Ravkin having incorporated therein, automated digitized imaging, processing, and storing of the labeled and identified fetal nRBCs, because Alter specifically suggested application of the MACS method in conjunction or combination with other cellular separation/enrichment methods. One of ordinary skill in the art at the time of the instant invention would have been motivated to combine the teaching of Alter which incorporates magnetic bead separation, with other fetal nRBC enrichment methods such as that taught by Ravkin, wherein fetal nRBCs are enriched and detected for further automated processing of digitized images, because Alter specifically taught that his method provides increased recovery yield of fetal nRBCs from the peripheral circulation of pregnant women, for use in prenatal diagnostic studies and purposes.

8. No claims are allowed.

Remarks

9. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Zheng et al. (Prenatal diagnosis from maternal blood: simultaneous immunophenotyping and FISH of fetal nucleated erythrocytes isolated by negative magnetic cell sorting, Journal of Medical Genetics, 30 (12): 1051-1056 (December 1993)) teach simultaneous immunophenotyping and FISH of fetal nucleated erythrocytes isolated by negative magnetic cell sorting (see Abstract).

Mavrou et al. (Fetal Nucleated Erythrocytes (NRBCS) in Chorionic Villus sample supernatant fluids: an additional source of Fetal Material for Karyotype Confirmation, Prenatal Diagnosis 17 (7): 643-649 (1997)) teach a method for simultaneously detecting a phenotype and a genotype of a heme-containing cell such as fetal nRBCs in a sample. First, the fetal nRBC is contacted with a [first] fluorophore labeled mouse anti-fetal hemoglobin antibody (UCHγ) which binds an antigen in the nRBC in order to provide an immunophenotype of the cell. The cell is further contacted with a [second] fluorophore labeled DNA X- and Y- specific probe for fluorescence in situ hybridization (Two-colour FISH) analysis in order to provide a genotype (karyotype) of the cell (see Abstract and page 644, columns 1 and 2).

Pazouki et al. (A rapid combined immunocytochemical and fluorescence in situ hybridization method for the identification of human nucleated red blood cells, Acta Histochemica, 98 (1): 29-37 (January 1996)) teach a rapid combined immunocytochemical and fluorescence in situ hybridization method for the identification of human fetal nucleated red blood cells (see Abstract).

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
September 30, 2005